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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,048	01/26/2006	Philipp Hadwiger	14174-109US1 RIB 016.2PCT	3878

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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
08/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/543,048	HADWIGER ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86,89,90,94-98,100-102 and 110-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86,89,90,94-98,100-102 and 110-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 86-105 in the reply filed on 06/13/2007 is acknowledged.

Status of the Application

Claims 86, 89, 90, 94-98, 100-102, and 110-119 are pending and currently under examination. Claims 1-85, 87-88, 91-93, 99 and 103-109 are canceled..

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, applicant cannot rely on the foreign priority document to overcome any prior art rejections because translation of the foreign priority document has not been made of record in accordance to 37 CFR 1.55

Information Disclosure Statement

The submission of the Information Disclosure Statement on 02/13/2006 is in compliance with 37 CFR 19.7. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 117 and 119 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 117 and 119 recites the limitation "the target gene". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 86, 89, 90, 94-98, 100-102, 110-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rana, T. (US 2005/0020521) in view of Florence et al. (Journal of Controlled Release, 2000, Vol. 65: 253-259), Manoharan, M. (20030064492, "Manoharan I") and Cook et al. (U.S. Patent No. 6,803,198) and evidenced by Manoharan, M. (Applicant's IDS 02/13/2006, "Manoharan II").

The instant claims are drawn to a dsRNA comprising a complementary RNA strand and a sense strand and only one lipophilic group having a logKow exceeding 1, 1.5, 2 or 3, wherein the lipophilic group is covalently attached to the 5' end of the complementary strand or the 5' end of the sense strand, wherein the dsRNA is complementary to a (+) strand RNA virus, wherein the linkages between the 5' comprises a phosphodiester group, wherein the linkage does not comprise a

phosphodiester group, wherein the lipophilic group is a sterol, cholesteryl or selected from the group as listed in claim 98, wherein the dsRNA has overhangs on one or both ends, wherein the dsRNA is between 16 to 30 nucleotides in length, wherein the target gene is expressed in cells as listed in claim 117 and wherein the dsRNA targets HCV.

Rana teach modified siRNA molecules wherein the modifications increase the stability of the molecule and enhance the cellular uptake of the molecule which is important for *in vivo* applications (see paragraph 0032). Rana teach modifications of the siRNA at the 5' end or 3' end or both the 5' and 3' ends (see paragraph 0033). Rana et al. teach the modifications comprise such compounds as peptides, nanoparticles or dendrimers, which are considered lipophilic groups (see paragraph 0033). Rana teach the siRNA is preferable from 10-50 nucleotides in length (see paragraph 0057) and teach the siRNA can comprise overhangs on the 5' or 3' ends wherein the overhangs are 1-4 nucleotides in length (see paragraph 0086) and further teach the siRNA can target any cell. Rana teach the siRNA can comprise a RNA strand that is complementary to a liver cell comprising a HCV target gene and reduce expression from said target gene (see paragraph 0206). Rana do not specifically teach the lipophilic group has a logKow i.e. an octagonal/water partition coefficient exceeding 1 and do not specifically teach the lipophilic group is a sterol, or carbamate linked cholesteryl or wherein said group is linked at the 5' end with a phosphodiester group.

Florence et al. teach a lipophilic dendrimers, PAMAM, are efficient drug delivery vehicle for molecules because the dendrimer is small and can translocate across the

cell layer (see page 254). Florence et al. teach such PAMAM dendrimers has an octagonal/water partition coefficient of 17.5 (see page 255).

Manoharan I teach methods of increasing the stability of an inhibitory nucleic acid and teach conjugation of lipophilic groups to the 5' or 3' ends enhances the cellular uptake of such molecules. Manoharan I teach such groups can be sterols, cholesterol and aromatic groups (see paragraph 0018). Manoharan I teach such conjugates can be attached to the 5' or 3'ends using linkers such as phosphorodiester (see paragraph 0018) as well as other linkers as described in paragraph 0039).

Cook et al. similarly teach methods of increasing the stability of an inhibitory nucleic acid and teach attaching a carbamate cholesterol group increases the stability of said molecules (see columns 5 and 6).

It would have been obvious to one of skill in the art to incorporate the PAMAM dendrimer taught by Florence et al. onto the 5' or 3' end of the dsRNA taught by Rana. One of skill in the art would have been motivated to use the dendrimer taught by Florence et al. given that Florence et al. teach said dendrimer is the optimal size that can be delivered to cells and can be efficiently used as a delivery vehicle to deliver molecules across the cell layer which increases the molecules bioavailability. One would have expected success at using the dendrimer taught by Florence et al. along with the dsRNA taught by Rana because Rana teach conjugation of dendrimers enhances the stability of said dsRNA and because Florence et al. teach efficient *in vivo* delivery of said dendrimer to cells and tissues, demonstrating the molecule can be used to deliver therapeutic molecules, such as nucleic acid drugs.

It would have been obvious to one of skill in the art to use a known oligonucleotide conjugate, such as a sterol or aromatic group or a cholesteryl carbamate, as taught by Manoharan et al. and Cook et al., to link to a dsRNA taught by Rana. Such oligonucleotide conjugates taught by Manoharan et al. and Cook et al. were known in the art at the time of filing of the instant application to efficiently conjugate to inhibitory molecules and further the field was replete with prior art demonstrating predictable results of increased stability and enhanced uptake of nucleic acid molecules. For example, Manoharan II summarizes the prior art and states "oligonucleotide conjugates have been evaluated in a wide range of cell culture and in vitro experiments" and "the value of conjugation chemistry has been clearly demonstrated bv these studies" and states further that oligonucleotide conjugates improve the pharmacokinetic properties of the oligonucleotide, such as binding affinity for the target and nuclease resistance such that one can synthesize an ideal drug with predictable results. Therefore, because the claimed oligonucleotide conjugates were known in the art at the time of the invention of the instantly claimed invention and because such conjugates were known to efficiently improve the cellular delivery of oligonucleotides and increase their affinity for the target gene as well as increase their resistance to nucleases, it would have been obvious to one skilled in the art to use the conjugates taught by Manoharan et al. and Cook et al. to achieve the predictable result of improvement in cellular delivery of nucleic acid molecules.

Thus, the instantly claimed invention would have been obvious to one of skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

KC
Examiner
Art Unit 1635

/Sean McGarry/
Primary Examiner
AU 1635